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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/20/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,573	SEKI ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-7 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of Group I (claims 1-7 and 10-14, fluorescent proteins) in Paper No. 11 is acknowledged.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1653.

3. Applicant's submission of formal drawings on May 20, 2003 has been received and entered.

Specification

4. The disclosure is objected to because of the following informalities:

The specification is objected to because Figure 2 discloses SEQ ID NO:1, which is disclosed as the structure in the vicinity of a multi-cloning site of the plasmid vector, and the application does not have a sequence disclosure (see 37 CFR 1.821 and the attached Notice to Comply with the sequence rules). In addition, a certified copy of the priority document has not yet been submitted.

Correction is required.

Claim Rejections - 35 USC § 112

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 and 10-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is directed to a method of producing a soluble protein domain by preparing two or more DNA fragments by partially digesting a DNA coding for a protein, expressing a fusion protein which is coded on each of said DNA fragments fused with a DNA encoding a functional protein exhibiting said function among two or more fusion proteins synthesized in step (b) and synthesizing the soluble protein domain in a cell free system, and the DNA is described solely by function and not structure. The specification on page 3 indicates that "many DNAs contained in a DNA library were fragmented simultaneously and ligated to a gene of a functional protein to express fusion proteins, thus the essential method step of ligating the DNA is omitted. The method steps as recited in the claims do not lead to the desired product because to go from item (a) to item (b) requires an additional step and to go from item (c) to (d) requires an additional step (see also the methods of claims 10 and 13 which are incomplete/not adequately describe).

Claim 10 recites a method for producing a soluble protein domain comprising method steps (a-e), however, these steps may not result in a soluble protein. Step (a) begins with constructing an expression vector, which expresses a fusion protein with a GFP thus, the protein in step (a) may already be soluble. In addition, item (a) describes a vector containing a DNA coding for a protein and a gene for said green fluorescent protein/derivative thereof, which does not describe a fusion protein as claimed in line 1 of item (a). Steps (b-e) comprise, preparing two or more DNA fragments for partial digestion, transforming *E. coli* with each DNA, isolating a transformed clone and recovers the DNA from the isolated transformed clone, recovering the DNA from the isolated transformed clone and then synthesizing the soluble protein domain. The omission of essential method steps between items (b) through (e) does not lead to the production of a soluble protein domain. In addition, the claimed step (e) does not guarantee that one of skill in the art performing this would be left with a soluble protein to be able to synthesize the soluble protein domain in a cell free system as required by step (f). Thus, the method steps recited in claim 10 are not adequately described and do not necessarily result in the desired product.

The claims are also directed to a GFP or derivative thereof and the specification does not describe any attributes or provide any structural information about the "derivative thereof" to demonstrate possession, as the claims encompass a large genus not adequately described. Therefore, for all these reasons the claimed invention lacks adequate written description.

6. Claims 1-7 and 10-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method that partially digests DNA fragments, does not reasonably provide enablement for a method for producing soluble protein domains because the method as claimed cannot be practiced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to:

I. Quantity of Experimentation Necessary:

Claim 1 is directed to a method of producing a soluble protein domain by preparing two or more DNA fragments by partially digesting a DNA coding for a protein, expressing a fusion protein which is coded on each of said DNA fragments fused with a DNA encoding a functional protein exhibiting said function among two or more fusion proteins synthesized in step (b) and synthesizing the soluble protein domain in a cell free system, and the specification on page 3 indicates that "many DNAs contained in a DNA library were fragmented simultaneously and ligated to a gene of a functional protein to express fusion proteins, thus the essential method step of ligating the DNA is omitted. The method steps as recited in the claims do not lead to the desired product because to go from item (a) to item (b) requires an additional step and to go from item (c) to (d) requires an additional step (see also the methods of claims 10 and 13 which lack

essential method steps as well). To practice the claimed invention as recited would require undue experimentation, because with the absence of essential method steps one of skilled in the art is left with an invitation to perform further experimentation.

II. Breadth of the claims/Amount of direction or guidance presented/Presence or absence of working examples:

The claims encompasses an unspecified amount of gfp derivatives and the specification provides no guidance/direction as to any attributes or characteristics they possess, for example, a structure. No working examples are provided to rectify the missing information. Additionally, as the method steps are incomplete one of skill in the would not be able to practice the invention as claimed absent specific guidance in the claims.

IV. Nature of the Invention/State of the prior art and Relative skill of those in the art/Predictability or unpredictability of the art:

The invention is directed to methods of producing soluble protein domains, however, the recited method steps cannot achieve this goal as essential method steps are missing. It is noted that the specification indicates that the DNA has to be ligated although the step is missing from the claims, however, the methods are missing other essential steps not described in the instant specification. The prior art cannot supplement the missing method steps because specific information is required to practice the claimed invention not the general knowledge in the art, thus is unpredictable.

Therefore, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-7 and 10-14 are rejected under 112, second paragraph as failing to distinctly point out the subject matter applicant regards as his invention.

Claims 1, 10 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: between step (a) and (b) and step (c) and (d) of claim 1 as it is unclear how a partially digested DNA encoding a protein leads to the expression of a fusion protein and how selecting a fusion protein leads to synthesizing a soluble protein domain (see also independent claims 10 and 13). See for example page 7 of the instant specification, where it is stated that "it is essential that the DNA fragments are properly ligated to a gene coding for a functional protein". As the limitations of the specification cannot be read into the claim, the method steps recited omits essential method steps. Note that in claim 10 (a) the method starts out with an expression vector which expresses a fusion protein with a gfp/derivative thereof and the expression vector is then said to comprise a DNA coding for a protein and a gene for gfp which are different than the starting materials of a fusion

protein. The claim is also indefinite because method steps (b-e) do not lead to the production of a soluble protein domain as claimed because essential method steps are missing (see also claim 13). The dependent claims are included in this rejection.

Claim 10 is indefinite for the recitation of "constructing a expression vector" instead of "constructing an expression vector".

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103 (a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

9. Claims 1-3, 10 and 13 are rejected under 35 U.S.C. 103(a) as obvious over Chien et al. (PNAS, vol. 88, pages 9578-9582, November 1991) in view of Waldo et al. (Nature Biotechnology, vol. 17, pages 691-695, 1999). The art has been broadly applied to the recited methods although essential method steps are missing to demonstrate that the present method steps are obvious.

The disclosure state that a partially digested DNA means using a DNA decomposing enzyme treatment such as Dnase I, various Restriction enzymes, Bal31, Exonuclease III and other generally known enzymes. (pages 6-7).

Chien et al. teaches cutting Gal4 into fragments with restriction enzymes (DNA decomposing enzyme, claim 2) and the expression of a fusion protein (claims 1 and 12), the fusion partner being lacZ, which has expressed function and is luminescent (claim 3), see page 9579. In addition, the reference teaches transforming *E. coli* with the DNA (claims 5, 6 and 10). Further, the specification states on page 8 that "solubility of proteins coded on the DNA fragments can be predicted. As a concrete example, they can be prepared using the reporter genes mentioned below, for example, a beta-galactosidase gene derived from *E. coli* (lac Z)", which functions as admitted prior art. In-so-far-as Chien et al. do not teach GFP, Waldo et al. teach GFP fusion proteins (claims 4 and 11) for the formation of folding robustness to improve soluble expression in *E. coli*. The Chien et al. and Waldo et al. references do not recite the use of a cell-free expression system for the production of a soluble protein domain, while Chien et al. and Waldo et al. use cell based systems. However, in vitro translation systems such as

reticulocyte lysate or wheat germ lysates for the production of polypeptides in a cell free system a well known in the art (see also pages 10-11 of the specification where it is stated that these are generally known). Use of such systems have the advantage over cell based systems that one has control over the particular proteins expressed within the system such that production of undesired enzymes, such as glycosyltransferases which would produce heterogeneity in an oligosaccharide synthesis) can be eliminated. As such it would have been obvious to one of skill in the art that the cell based system as disclosed by the references can be substituted for the cell free systems recited in the claims with a reasonable expectation of success (claim 7).

Therefore, it would have been obvious to one of ordinary skill in the art to obtain the invention as a whole because Chien et al. partially digests DNA with restriction enzymes, and expresses a fusion protein (with function) and Waldo et al. teach folding robustness using GFP fusions and partially digested DNA via restriction enzymes. One of ordinary skill in the art would be motivated to combine the teachings of the references because it is known in the art that GFP is a reporter of gene regulation and Waldo et al. teach the advantages of using GFP to obtain soluble domains. Therefore, at the time of filing the claimed invention was obvious to make and use.

10. Claims 10-14 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Waldo et al.(Nature Biotechnology, vol. 17, pages 691-695, 1999). The art has been broadly applied to the recited methods although essential method steps are missing to demonstrate that the present method steps are obvious.

Waldo et al. teach DNA encoding a protein of function that is subjected to DNA shuffling which is equivalent to a partial digest (claim 12) as a restriction enzyme is used to cut the DNA into fragments (claim 10, page 692). The reference also teach the construction of a folding reporter vector (claim 13) in which a test protein is expressed as an N-terminal fusion with GFP in *E. coli* (claim 10 page 691). Waldo et al. teach that a plurality of proteins were used a panel of 20 test proteins (abstract, claim 11). The reference also teach testing to ensure that there is no loss of function (claim 13). The reference teach the production of a soluble protein domain, however, does not teach a cell free system. The Waldo et al. reference does not recite the use of a cell-free expression system for the production of a soluble protein domain, while Waldo et al. use cell based systems. However, in vitro translation systems such as reticulocyte lysate or wheat germ lysates for the production of polypeptides in a cell free system are well known in the art (see also pages 10-11 of the specification where it is stated that these are generally known). Use of such systems have the advantage over cell based systems that one has control over the particular proteins expressed within the system such that production of undesired enzymes, such as glycosyltransferases which would produce heterogeneity in an oligosaccharide synthesis) can be eliminated. As such it would have been obvious to one of skill in the art that the cell based system as disclosed by the references can be substituted for the cell free systems recited in the claims with a reasonable expectation of success (claim 7).

Therefore, it would have been obvious to one of ordinary skill in the art to obtain the invention as a whole because Waldo et al. partially digests DNA with restriction enzymes, expresses a fusion protein (with function) and teach folding robustness using GFP fusions. Additionally, Waldo et al. teach the advantages of using GFP to obtain soluble domains. Therefore, at the time of filing the claimed invention was *prima facie* obvious.

Conclusion

11. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday-Friday from 9:00 am to 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please

affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope Robinson, MS

Patent Examiner

CHRISTOPHER S. F. LOW
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